Claims

We claim:

1. A crystal composition comprising a ternary complex of a compound, a protein, and a poly-nucleic acid wherein the protein is covalently linked to a phosphorous of the poly-nucleic acid.

2. A crystal composition of claim 1, wherein the compound is an inhibitor of a topoisomerase.

3. A crystal composition comprising a complex of a compound and topoisomerase covalently linked to a poly-nucleic acid substrate.

4. A crystal composition of claim 3 wherein the protein is a eukaryotic topoisomerase.

5. A crystal composition of claim 3, wherein the nucleic acid is DNA.

6. A crystal composition of claim 3, wherein the nucleic acid is duplex DNA.

7. A crystal composition comprising a complex of a compound and human topoisomerase I covalently linked to a duplex DNA substrate.

8. A crystal composition of claim 7, wherein the compound is an inhibitor of a topoisomerase.

9. The crystal composition of claim 7 wherein the crystal structure is crystal Form 7, Form 8, Form 9, Form 10, or Form 11.

10. A three-dimensional structure of a fully active form of human topoisomerase I in complex with duplex DNA (Form 7).

11. A three-dimensional structure of a compound contacting human topoisomerase I in covalent complex with duplex DNA.

12. The structure of claim 11 in which the compound is topotecan in the crystal Form9-TTC.

13. The structure of claim 11 in which the compound is AG260 in the crystal Form9-AG260.

14. The structure of claim 11 in which the compound is MJ-II-38 in the crystal Form 10.

15. The compound of claim 11 in which the compound is Hoechst-33342 in the crystal Form 11.

16. A method for identifying an agent which is an inhibitor of human topoisomerase I comprising:
(a) contacting the agent with topoisomerase I covalently linked to a duplex DNA substrate to form a complex;

(b) growing a crystal of the complex and isolating the crystals of complex; and

(c) determining the three-dimensional crystal structure of the complex.

17. The method of claim 16 wherein novel compounds are tested to see if crystal structures are formed.

18. Novel compounds which complex and form a crystal structure in accordance with the method of claim 16.

19. A process for designing an inhibitor of a topoisomerase comprising:
(a) forming a crystalline composition of a compound and topoisomerase covalently bound to duplex DNA.
(b) solving the three-dimensional structure of the crystalline composition;
(c) employing said three-dimesional structure to design or select a potential inhibitor;
(d) contacting said potential inhibitor with said topoisomerase in the presence of a substrate to determine the ability of said potential inhibitor to inhibit said topoisomerase.

20. A novel inhibitor of topoisomerase designed by the process of claim 19.

21. A inhibitor according to claim 20 which is an anti-cancer agent.

22. A inhibitor according to claim 20 which is an anti-microbial agent.

23. A inhibitor according to claim 20 which is an anti-viral agent.

24. The use of a topoisomerase and DNA to crystallize and determine the three-dimensional structure of a DNA binding agent.

25. A crystallant solution composed of: 8-13% (w/v) PEG-8000; 50-200 mM buffering agent at pH 6.3 to 6.6; 150-250 mM lithium sulfate, to

crystallize and solve the 3-D structures of complexes composed of human topoisomerase I, DNA and a compound.

26. The crystallant solution of Claim 25 wherein the buffering agent is MES-NaOH.

27. The crystallant solution of Claim 25 wherein the buffering agent is ADA-NaOH.